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EXAMINER	
MANOHAR, MANU M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,121	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	MANU M. MANOHAR	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49 and 57-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49 and 57-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTIION

Status of the Application

This Office Action is in response to applicant's arguments filed on January 18, 2009. **Claims 49, 57-64 are pending and the claims 49, 57-64 are examined herein.**

The applicant's statement regarding the priority and Information Disclosure Statement is noted and acknowledged. The applicant argument regarding the rejections of the claims 49, 57-64 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is found to be persuasive and the rejections are withdrawn.

The applicant argument regarding the rejections of the claims 49, 57-64 under 35 U.S.C. 103(a) as being unpatentable over D' Amato [US Patent 6,469,045, in view of Wolff (Wolff, M.E. *Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, **1979**, 336-337), in view of Bilodeau et al (US Application Number US 2002/0137755) and in view of Kovesdi et al (US Application Number US 2002/0137755) found to be not persuasive and the rejections of the last Office Action are maintained.

Hence all the rejections of the claims under 35 U.S.C. 103(a) are maintained for reasons of record and modified and repeated below for Applicant's convenience. In addition new rejections are made based on the new grounds as set forth below in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed. Claim 58 is drawn to a method of treating macular degeneration comprises administering a compound recited in claim 49 and the method comprises administering a second active agents including a xanthine derivative. While the examiner acknowledges the listing of various second agent like steroids, antioxidants, antibiotics (specification page 6 line 23-30) the specific descriptions of a xanthine derivative is not defined by the instant specification. As such, the disclosure of the instant specification is not sufficient to support the use of second active agent a xanthine derivative and requires further description and clarification.

Claims 49 and 57-61, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, or salts thereof, does not reasonably provide enablement for a solvate. Claims 49 and 59 recites the use of compounds or a pharmaceutically acceptable solvate for the method of treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ 2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factor to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

1) The breadth of the claims: The breadth of the claims includes all of the hundreds solvates of compound as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is too broad and that is not supported by the specification.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." In re Rainer, 146

USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

2) The nature of the invention: The invention is the methods of using compositions comprising immunomodulatory compounds for treatment and management of macular degeneration. The invention discloses the method comprises administering to a patient a therapeutically effective amount of compound of the formula in claim 49 or a pharmaceutically acceptable salt, solvate therof. The invention also discloses in claim 59 a second active agent like thalidomide or pharmaceutically acceptable salt therof. The formula in the claim 49 and a second active agent in claim 59 encompass a number of compounds and embraces undefined number of variables and there is no teaching of any hydrate or solvate of this compound.

3) The state of the prior art: Search in the pertinent art, including water a solvent resulted in a pertinent references, which is indicative of unpredictability of solvate and hydrate formation in general. The state of the art is that it is not predictable whether solvates or hydrates will form or what their composition will be.

Vippagunda et al (Advanced Drug Delivery Reviews,48, 3-26, 2001), which clearly states that formation of solvates is unpredictable. See entire document, especially page 18, left column: section 3.4. Vippagunta et al states, "Each solid compound responds uniquely to the possible formation of solvates or hydrates and, hence, generalizations cannot be made for series of related compounds."

Byrn, et al. (Solid State Chemistry of Drugs, 1999), teach that "the occurrence of hydrated or solvated crystal forms, crystals in which solvent molecules occupy regular positions in the crystal structure, is widespread but by no means universal among drug substances (pg 232). Most drug crystals that fall into the category of solvates are hydrates (pg 236). Byrn, et al note that the water molecule is particularly suited to fill structural voids, due to its small size. In hydrated crystal structures, water molecules bind to other water molecules but also to any available functional group, i.e. carbonyls, amines, alcohols, and many others which are capable of accepting or donating an active hydrogen atom to form hydrogen bonds (pg 236, "Hydrates"). The behavior of hydrates of pharmaceuticals is unpredictable due to dehydration prior to melting, and cracking during dehydration (pg 234). Also hydrates and solvates may only be formed under certain conditions, dependent upon the compounds sought to be crystallized. Such a process is not a given in pharmacology and requires a great deal of research, with no reasonable expectation of success.

4) The amount of direction provided by the inventor: There is lack of enough guidance and direction to practice the invention – preparation of the solvates and hydrates of the instant compounds recited in claim 49 and in claim 59, in the specification of the application. Preparation of solvates comprising the use different kind of solvents and the result would be unpredictable. Guidance for preparing and using of all the possible combinations reagent is not provided in the instant specification for preparation of solvates.

5) The level of predictability in the art: The state of the art is that is not

predictable whether solvates will form or what their composition will be. In the language of a chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R. "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

6) The existence of working examples: Determining if any particular substrate would form a solvate, or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, and other parameters. The experimentation is potentially open- ended. The application fails provide working example, guidance or direction as to how to making the solvate and hydrate encompassed herein. As was stated in Morton International Inc. v. Cardinal Chemical

Co., 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ...there, is no evidence that such compounds exist.., the examples of the patent do not produce the postulated compounds.., there is... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. There should be some showing supporting that solvates of these compounds exist and therefore can be made.

7) The quantity of experimentation necessary: In the chemistry art it is not usually possible to predict the nature of the solvates and hydrates, whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. Indeed, one of ordinary skill in the art could not ascertain which solvates or hydrates would form with any reasonable expectation of success. The instant specification does not make up for this deficiency, as there is no guidance to an ordinarily skilled artisan to either make a solvate or hydrate of the claimed compound for the treatment of parasitic disease in animal. Undue and unpredictable experimentation would be required to use the invention as claimed. Therefore, the instant specification and prior art would not enable one of ordinary skill in the art at the time the invention was made to make and use the invention commensurate with the scope of the rejected claims.

8) The relative skill of those in that art: The relative level of skill possessed by

one of ordinary skill in the art of research is relatively high, as a majority of lead investigators conducting scientific research and development in this particular area possess M.S. and/or Ph.D. in a scientific discipline such as medicinal chemistry, biochemistry, pharmacology, organic synthetic chemistry or the like.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The claims 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention The claim 58 is not clear about identifying a second active agent a xanthine derivative in the composition for treating macular degeneration. It is not distinctly defined by the term derivative since it embraces indefinite number of compounds. The online reference dictionary defines "derivative" as, "a chemical substance or a compound derived from or obtained from another substance or compound". Therefore, the definition of derivative in the dictionary does of xanthine derivatives not shed light on what Applicants' intended for the meaning

The claim 59 is not clear about identifying a solvate of second active agent in the composition for treating macular degeneration. It is not distinctly defined by the term solvate since it embraces numerous numbers of very different compounds. Vippagunda et al (Advanced Drug Delivery Reviews, 48, 3-26, 2001) clearly states that formation of

solvates is unpredictable (page 18, left column: section 3.4). Vippagunta et al further states, "Each solid compound responds uniquely to the possible formation of solvates or hydrates and, hence, generalizations cannot be made for series of related compounds." Hence the term solvate is indefinite and not distinctly defined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 49, 57-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over D' Amato, US Patent 6,469,045 (listed in Information Disclosure Statement) as evidenced by Wolff, (Wolff, M.E. *Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, 1979, 336-337) in view of Bilodeau et al (US Application Number

US 2002/0137755) and in view of Kovesdi et al (US Application Number US 2002/0137755)

The invention is the method of using compositions comprising immunomodulatory compounds for treatment and management of macular degeneration. The claims disclose the method comprises administering to a patient a therapeutically effective amount of compound of the formula in claim 49. The claims further disclose a second active agent in the composition for treating macular degeneration and intervention like surgery.

D' Amato teaches a compound without a methyl group with the exact same core structure as claimed in the instant claims (Figure 1, 2nd formula in the top from left). In addition D' Amato discloses the compound with the same core structure as an example (cool 17 compound EM-12) for the inhibition of corneal revascularization (macular degeneration) (col 16 Example III). The instant compounds claimed in the claim 49 and the compound disclosed by D' Amato et al are homologues to each other and it is *prima facie* obvious to use one compound over another. The compounds differ only methyl (alkyl) group in the aromatic ring and possess same functional property unless evidences are shown to contrary and unexpected results. Examiner enclosed a document which discloses that H and alkyl group in an aromatic ring of a compound are interchangeable and the compound possess the same property as evidence. (examples in Table 8.2 of a local anesthetic SAR pg. 337 of Wolff, M.E. *Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, **1979**, 336-337)

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re*

Opprecht 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

D' Amato also teaches the treatment of ocular neovascular diseases associated with angiogenesis (Column 1 line 65-66) including macular degeneration (column 2 lines 3-6 and 25) with antiangiogenesis compounds like thalidoamide derivatives 9 (col 1 lines 22-24). D' Amato further teaches several categories of macular degeneration like Best's disease, Stargardt's diseases, neovascularization and retinopathy (Col 2 lines 23-39, col 21 claim 68). Furthermore D' Amato teaches the preparation of enrichment of optically active enantiomers, thus stereomerically pure compounds (Column 12 line 34-46).

D' Amato et al does not disclose the use of a second active compound for the treatment and also does not teach the surgical intervention directed at reducing the symptoms of macular degeneration.

Bilodeau et al teaches the use of therapeutically effective amount of several second compounds (Page 63 claims 30 and 32) like interferon, antibody to VEGF, steroid, anti-inflammatory compound for diseases related to angiogenesis including macular degeneration (page 63 claim 22).

Kovesdi et al teaches the several intervention methods including surgical intervention along with other ocular therapies like photodynamic therapy (light therapy),

photocoagulation laser therapy, macular translocation or surgery (Page 10, paragraph [0066]) for treating macular degeneration. It further teaches the intervention can be a part of other treatment regimen which teaches that the intervention can be before, during or after intervention as claimed in instant claim 63.

It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Therefore it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the instant invention to adapt the method of treating the disease like macular degeneration as taught by D' Amato with a second active compound as taught by Bilodeau et al with surgical interventions as taught by Kovesdi et al.

One of the ordinary skills in the art would be motivated to adapt the method of treating the disease like macular degeneration as taught by D' Amato with a second active compound as taught by Bilodeau et al with surgical interventions as taught by Kovesdi et al. 1) D' Amato also teaches the treatment of ocular neovascular diseases associated with angiogenesis including macular degeneration with compounds like thalidoamide derivatives including a homologue compound of the instant invention. 2) Bilodeau et al teaches the use of several second compounds like interferon and steroid for the treatment of macular degeneration. 3) Kovesdi et al teaches the surgical intervention along with other ocular therapies like laser therapy or surgery for treating

macular degeneration. Moreover the prior arts disclose the composition with the same ingredients and use of composition for treatment specifically for macular degeneration as claimed in the instant invention. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in adapting the method of treating the disease like macular degeneration as taught by D' Amato with a second active compound as taught by Bilodeau et al with surgical interventions as taught by Kovesdi et al.

Response to Arguments to rejection under 35 U.S.C. 103(a)

Applicant's arguments against the 35 USC 103 rejections of the claims 49, 57-64 have been fully considered but found not persuasive. The rejections over over D' Amato [US Patent 6,469,045] in view of Wolff (Wolff, M.E. *Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, **1979**, 336-337), in view of Bilodeau et al (US Application Number US 2002/0137755) and in view of Kovesdi et al (US Application Number US 2002/0137755) found to be not persuasive and the rejections of the last Office Action are maintained and modified rejection are as set forth above.

The applicants argue that D' Amato et al do not disclose the exact compound as claimed in the instant invention and the cited reference have not provided a reason to select the claimed compound. The applicant also argue that the teaching of the prior arts Bilodeau et al and Kovesdi et al would not have provided a reasonable expectation of success. The applicants further state that the Examiner has not established a *prima facie* obviousness and D' Amato et al do not teach the specific compound hence there are no obviousness over the teachings of neither Bilodeau et al nor Kovesdi et al.

The Examiner confirm as set forth above with the modified U.S.C 103 (a) rejections that the instant compound claimed in the invention and the compound disclosed by D' Amato et al are homologues and differ only with methyl group and it is obvious to one of ordinary skill in the art to use the homologue for the same purpose, here for treating macular degeneration, unless teachings are present to contrary. In addition D' Amato teaches the use of the same disclosed compound as an example for treating macular degeneration and hence provide evidence for the reasonable expectation of success. Since D' Amato et al teaches the specific compound it would be obvious to one of ordinary skill in the art over the teachings of Bilodeau et al and Kovesdi et al to use it in the method of D' Amato et al. Furthermore Bilodeau et al and Kovesdi et al teaches the ingredients and step specifically for treating macular degeneration and the applicants also recite the same method of treatment for the disorder, macular degeneration, hence *prima facie* obviousness is clearly established.

It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusions

Claims 49, 57-64 are stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MANU MANOHAR whose telephone number is (571)270-5752. The examiner can normally be reached on Mon - Thu 9.00AM to 4.00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-270-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MANU MANOHAR
Examiner
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